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Radiotherapy for Locoregional Recurrent Non-Small Cell Lung Cancer

Purpose: To retrospectively evaluate the outcomes and complications of curative radiotherapy for locoregionally recurrent non-small cell lung cancer (NSCLC). **Materials and Methods:** From 2004 to 2008, 21 patients received curative radiotherapy for locoregionally recurrent NSCLC without systemic metastasis after surgery. At the time of recurrence, the median age was 70 years (range 49～81 years), and 19 patients were male. Most patients (n=17) were ECOG 0 or 1 performance status. The median disease-free interval was 15 months. Distribution of recurrence sites were mediastinal lymph nodes (n=10), ipsilateral hilar lymph nodes (n=4), ipsilateral lung parenchyma (n=4), bronchial stump (n=2) and ipsilateral supraclavicular lymph nodes (n=1). Radiotherapy was administered (median 66 Gy, range 59.4～70 Gy) by a three-dimensional conformal technique. Thirteen patients received chemotherapy concurrently during radiotherapy. Pulmonary function test (PFT) was also used to detect lung function change before and after radiation. **Results:** The median survival and 1- and 2-year survival rates were 17 months, 68% and 34%, respectively. Concurrent chemotherapy did not affect post-recurrence overall survival (p=0.183). Seven patients (33% of all patients) had re-progression within the radiation field at a median time of 4 months after completion of radiation. Diffusing lung capacity for carbon monoxide of lung after radiotherapy decreased significantly compared with pre-radiotherapy status (p=0.033). Radiation pneumonitis of any grade was seen in 11 patients. Three patients died of pulmonary complications: one of bacterial pneumonia, one of exacerbation of underlying interstitial pulmonary fibrosis and one of radiation pneumonitis. **Conclusion:** This retrospective study showed that curative radiotherapy for locoregionally recurrent NSCLC resulted in a median survival of 17 months and a 2-year survival rate of 34%, which is comparable to other studies. Patients suitable for curative radiotherapy for recurrent NSCLC could be treated aggressively, such as using high dose radiation with or without chemotherapy. However, pre-radiotherapy lung function should be carefully evaluated to avoid serious post-treatment lung damage considering poor lung function of post-resection patients. **(J Lung Cancer 2011;10(1):37－43)**

Key Words: Non-small cell lung carcinoma, Local recurrence, Radiotherapy

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INTRODUCTION

Lung cancer remains the leading cause of cancer related death in the world. Surgery is the treatment of choice for stage I or II non-small cell lung cancer (NSCLC), including selected stage III NSCLC. Despite complete resection of NSCLC, 15～30% of patients experience locoregional recurrence (1-4). Because locoregional recurrence has an impact on achieving cure and overall survival (OS) for patients with early stage NSCLC, appropriate subsequent treatments are needed. Although some patients are treated with re-operation, salvage

re-operation is limited to select patients (5,6). Radiotherapy and/or chemotherapy are commonly used for isolated locoregional recurrence of NSCLC after surgery. Several retrospective studies have reported a median OS of 10～20 months in these patients (7-10). Documented prognostic factors that influence survival are variable, and include disease-free interval (DFI), sites of recurrence, aim of treatment (curative vs. palliative) and use of chemotherapy. Several studies have reported comparable survival of patients with post-resection recurrent NSCLC to that of newly diagnosed NSCLC, when both groups of patients are treated with curative radiotherapy or chemoradiotherapy (11,12). These investigators suggested that patients with post-resection locoregional recurrent NSCLC should be treated aggressively to achieve a cure.

When considering curative radiotherapy for recurrent NSCLC after surgical resection, pulmonary function should be carefully evaluated to avoid serious lung damage, because these patients already have compromised lung function due to surgical resection of lung at initial diagnosis of NSCLC. Even if lung function is normal post-operatively, declined lung function after salvage radiation can occur. While several studies have reported on the survival rates of curative radiotherapy for locoregional recurrent NSCLC, little data exists concerning lung complications after salvage radiation.

Thus, this retrospective study was performed to clarify the outcomes of curative radiotherapy for patients with locoregional recurrent NSCLC. In addition, lung complications and changes of pulmonary function were retrospectively evaluated before and after salvage radiotherapy in these patients.

MATERIALS AND METHODS

1) Patient identification

From 2004 to 2008, 21 patients received curative radiotherapy for locoregional recurrent NSCLC at Seoul National University Bundang Hospital. All patients who were selected for this study received curative surgical resection at initial diagnosis of NSCLC, and did not receive postoperative adjuvant radiotherapy. Initial surgery included lobectomy (n=16), pneumonectomy (n=3), bilobectomy (n=1), and wedge resection (n=1). Sixteen patients had adjuvant chemotherapy after surgical resection. Loco-regional recurrence was defined as a relapse in anatomically contiguous sites to primary tumor or regional lymphatics.

Recurrence was diagnosed through computed tomography (CT), fluorodeoxyglucose-positron emission tomography (FDG-PET) or any abnormal findings on bronchoscopy. Five patients were pathologically confirmed by bronchoscopic biopsy. Patients who had synchronous distant metastasis at the time of recurrence were excluded from this analysis. Synchronous distant metastasis was defined as distant metastasis within 6 months or at the same time as loco-regional recurrence. Table 1 shows the patients' characteristics. Briefly, median age at diagnosis of recurrence was 70 years (range, 49～81 years), and most patients were male (n=19). The median DFI was 15 months. Median duration of follow-up for all patients and survivors was 14 months and 17 months, respectively.

Table 1. Characteristics of the Patients

Variables	Patients
Age*, yr	70 (49～81)
Gender	
Male	19 (91)
Female	2 (9)
Histology	
Squamous cell carcinoma	11 (54)
Adenocarcinoma	5 (23)
Other	5 (23)
Performance status	
ECOG 0～1	17 (82)
ECOG 2	4 (18)
Disease free interval, mo	15†
≥15	10 (45)
<15	11 (55)
Recurrence site	
Mediastinal lymph node	10 (45)
Hilar lymph node	4 (18)
Lung parenchyma	4 (18)
Bronchial stump	2 (9)
Supraclavicular lymph node	1 (5)
Initial stage	
I	8 (38)
II	4 (19)
IIIA	5 (24)
IIIB	4 (19)
Recurrence stage	
I	4 (18)
II	6 (28)
IIIA	9 (45)
IIIB	2 (9)

Values are presented as number (%) unless otherwise indicated.
*Median age (range), †Mean months.
ECOG: Eastern Cooperative Oncology Group.

2) Radiotherapy

All patients had received irradiation for curative aim using a three-dimensional conformal technique. CT simulation with free breathing was performed with proper immobilization device. Gross tumor volume (GTV) was delineated on an axial CT scan in a pulmonary or mediastinal window setting. Except for lung parenchymal lesions, most GTVs were defined on CT scan in the mediastinal window setting. Clinical target volume (CTV) was created by expanding the GTV by a 5～8 mm margin, and approximately 10 mm was added to determine planning target volume (PTV). Hilar, mediastinal, and supraclavicular areas that appeared uninvolved on CT or FDG-PET were purposely not irradiated. Irradiation (median, 66 Gy; range, 59.4～70 Gy) was administered with 6～15 MV photons from linear accelerators. There were no differences of radiation dose prescription and target volume delineation between recurrence stage I-II and stage III disease.

3) Chemotherapy

Thirteen patients received concurrent chemotherapy during radiotherapy (CCRT). Most patients (n=12) received weekly cisplatin and paclitaxel during radiotherapy. Eight patients (72%) of recurrence stage III and five patients (83%) of recurrence stage II had received chemotherapy. On the other hand, no patient with recurrence stage I had chemotherapy during salvage radiotherapy. Compared with patients who did not receive chemotherapy, patients who received chemotherapy tended to be younger (p=0.001). All patients ＜70-years-of-age received chemotherapy, while only one patient ＞70-years-of-age did. None of the patients had consolidation chemotherapy after radiotherapy.

4) Statistical analysis

OS duration was calculated from the date of diagnosis of recurrence to time of death or last follow-up. OS and rates of progression-free survival (PFS) and local progression-free survival (LPFS) were estimated using the Kaplan-Meier method. The differences of patients' characteristics between the CCRT and radiation-only groups were estimated using Chi-square test. Several factors such as age, stage, performance status, DFI, higher radiation dose, and use of chemotherapy were evaluated as prognostic factors using the log-rank test, and the Cox regression model was used for multivariate analysis. Treatment-related toxic effects were assessed by Common Terminology Criteria for Adverse Event v3.0 (CTCAE-v3.0).

RESULTS

1) Survival and prognostic factors

Median survival was 17.4 months. The 1-year and 2-year OS rates were 68% and 34%, respectively (Fig. 1). There was no difference of survival rates between recurrence stage I-II and stage III disease (p=0.291). The 2-year OS rate of the CCRT group and the radiation alone group was 49% and 16%, respectively, but did not reach statistically significant level (p=0.183) (Fig. 2). The other potential prognostic factors, such as age (＜70 or ≥70 years), performance status, gender, DFI, and radiation dose (＜66 Gy or ≥66 Gy) were analyzed for

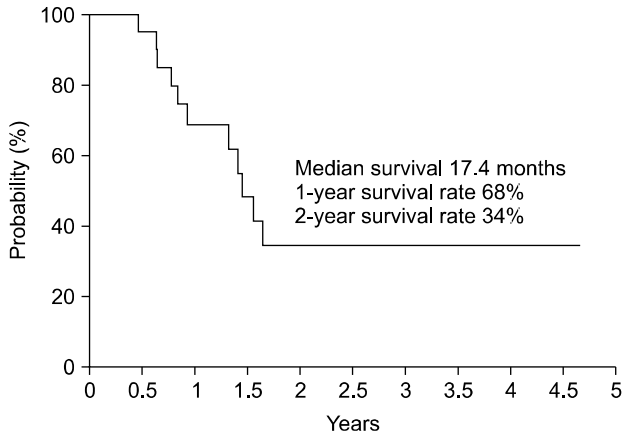

Fig. 1. Overall survival rate.

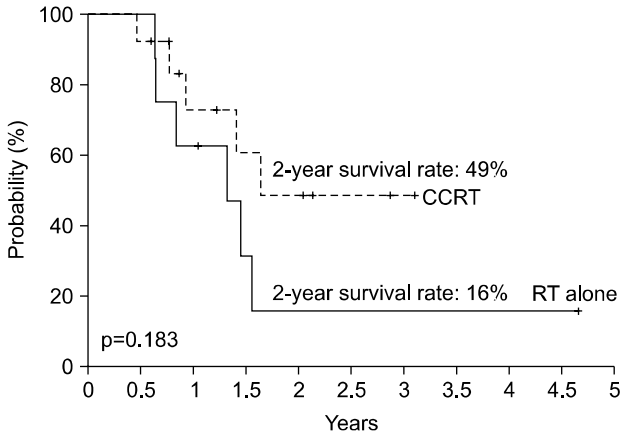

Fig. 2. Overall survival rate according to the use of chemotherapy. CCRT: concurrent chemoradiotherapy.

Table 2. Analysis of Prognostic Factors

Factor	p-value*	p-value†
Age, yr (<70 vs. ≥70)	0.406	0.727
Stages on recurrence (III vs. I~II)	0.291	0.060
DFI, mo (<15 vs. ≥15)	0.556	0.195
Concurrent chemo-radiotherapy or not	0.183	0.956
Radiation dose (<66 Gy or ≥66 Gy)	0.698	0.058

*Univariate analysis by log-rank test, †Multivariate analysis by Cox regression model.

Table 3. Changes in Lung Function

	FEV_1		DLCO	
	Mean value	p-value	Mean value	p-value
Pre-Op*	2.41		17.64	
Pre-RT	1.893	}0.312	14.529	}0.033
Post-RT	1.821		12.524	

*Baseline pulmonary function test before initial operation. FEV_1: forced expiratory volume in one second, DLCO: diffusing lung capacity for carbon monoxide.

their effect on survival. None of these factors was significant on univariate analysis (all $p>0.05$). Table 2 shows the results of the multivariate analysis. Recurrence stage I-II and radiation dose >66 Gy were of borderline significance as a prognostic factor (p=0.060 and 0.058, respectively).

2) Treatment failure

The 1-year and 2-year PFS rate was 58% and 41%, respectively. Radiation dose >66 Gy and use of chemotherapy did not increase PFS significantly (p=0.938 and 0.227, respectively). Twelve patients (57%) had experienced treatment failure after completion of salvage radiation. Of these 12 patients, seven patients had re-progression within radiation field at median of 4 months (range, 2~8) after radiation. The 2-year LPFS rate was 61%. A radiation dose >66 Gy did not affect LPFS (p=0.495). Of the seven patients, five died of local disease progression, and one died of distant progression following local progression within the radiation field. Distant progression developed at the brain (n=2), liver (n=1), bone (n=1), and multiple retroperitoneal, aortocaval, gastric lymph node (n=1). Two patients died of distant progression of disease.

3) Changes in lung function

All patients had pulmonary function test before and after salvage radiation. The mean values of forced expiratory volume in one second (FEV1) at pre- and post-radiation were 1.893 and 1.821, respectively. Mean value of diffusing lung capacity for carbon monoxide (DLCO) after radiotherapy decreased significantly compared with pre-radiation (p=0.033) (Table 3). When compared with pre-operation status (baseline lung function before initial surgery of NSCLC), the mean values of FEV1 and DLCO in pre-radiotherapy status decreased, but were not statistically significant.

4) Complications

Radiation pneumonitis of any grade was evident in 11 patients (52%). Only two patients had radiation pneumonitis of grade 3. These two patients were treated with steroid therapy and recovered gradually. There were three deaths related to pulmonary complications at 3, 5, and 6 months after completion of radiation. These pulmonary complications were caused by radiation pneumonitis in one patient, bacterial pneumonia in one patient, and exacerbation of underlying interstitial pulmonary fibrosis in one patient.

Radiation esophagitis of any grade during salvage radiation was evident in 13 patients (62%). Five patients experienced grade 2 esophagitis and one patient experienced grade 3 esophagitis, which required intravenous fluid support during salvage radiotherapy. All six patients had recurrence of the disease in the mediastinal lymph nodes located close to the esophagus.

DISCUSSION AND CONCLUSION

In this retrospective study of patients with locoregional recurrent NSCLC treated with curative radiotherapy, the patients had a median survival time of 17 months and a 2-year survival rate of 34%. These results are comparable to a previously published series. Leung et al. reported the median survival of 10 months of 45 patients with locoregional recurrent NSCLC (7). Patients treated with higher radiation dose (>50 Gy) had better outcome than patients treated with palliative intent radiation (p=0.02, median survival 16 vs 4.0 months, respectively). Another study analyzed 32 patients with locoregional recurrent NSCLC who were treated with radiotherapy (47.5~60 Gy); median survival and 2-year survival rate was 14 months and 28.1%, respectively (8). Complete response to

radiotherapy was shown to be a good prognostic indicator of survival. Foo et al. reported that median survival of patients treated with radical intent radiotherapy was 26 months, compared to 10.5 months for patients treated with palliative intent (p=0.025) (9). Most patients had partial or complete resolution of symptoms. They reported a longer DFI; performance status and radiation dose did not affect survival significantly. In the study of Jeremic et al., median survival and 2-year survival rate of patients treated with curative intent (dose, 55～60 Gy) was 18 months and 36%, respectively. Both median survival and 2-year survival rate were significantly different between curative intent and palliative intent (18 vs. 7 months and 36% vs. 11%, respectively; p=0.000) (10). A study comparing patients with post-resection locoregional recurrence of NSCLC with unresected NSCLC patients used median radiation doses of 56 Gy for recurrent disease and 59 Gy for newly-diagnosed disease (11). The median survival and 2-year actuarial survival rate was 12 months and 22% for recurrent disease, respectively, as compared to 12 months and 26%, respectively, for newly- diagnosed cases (p-value was non-significant). Patients with bronchial stump lesions had a median survival of 36 months, which was a superior outcome to those with nodal or chest wall recurrence (median survival of 9 and 7 months, respectively). The authors suggested that selected patients with post-resection loco-regional recurrence should receive aggressive treatment, equally to patients with newly-diagnosed NSCLC. Cai et al. also compared the survival of post-resection recurrent vs. newly-diagnosed NSCLC patients treated with radiotherapy and/or chemotherapy (12). These findings also suggested that patients with recurrent NSCLC after surgery should be treated aggressively. For stages I～III, no significant difference was observed in OS between post-resection recurrent patients and newly-diagnosed patients. Use of chemotherapy was analyzed as a prognostic factor for 5-year PFS in multivariate analysis (hazard ratio, 0.45; p=0.027). These findings also suggested that patients with recurrent NSCLC after surgery should be treated aggressively.

Previous studies reported mixed findings concerning prognostic factors. For example, several studies linked bronchial stump recurrence with increased survival (7,11), while another study failed to find such an association (9). On the other hand, many previous studies have similarly demonstrated that higher radiation dose of curative intent was beneficial to post-resection isolated loco-regional recurrent NSCLC. In the present study, a higher radiation dose was of borderline significance as a prognostic factor of post-recurrence OS. In addition, seven patients (33% of all patients) experienced treatment failure within the radiation field. These locally progressive tumors within the radiation field might have had an aggressive characteristic that would require a higher radiation dose for local control. Many radiation oncologists suspect the positive dose-response relationship between radiation dose and local control. If higher radiation dose could be administered without severe toxicity, improvement of treatment outcome could be expected. However, these results cannot be conclusive, because this study was limited due to its retrospective design and small patient population. In the case of newly-diagnosed NSCLC, radiation dose escalation can confer a survival benefit (13,14). Therefore, to determine beneficial effect of higher radiation dose, a prospective study is needed.

The role of chemotherapy in isolated locoregional recurrent NSCLC has not been well established. For newly diagnosed unresectable stage III NSCLC, combined treatment modality (concurrent chemoradiotherapy) had superior outcome compared with radiation alone (15-19). There have also been several reports indicating that adjuvant chemotherapy for patients with completely resected NSCLC improves survival (20,21). One of the aforementioned studies reported that use of chemotherapy affects PFS significantly, but does not confer a significant difference in OS (12). In our study, the 2-year OS rates of the CCRT group and the radiation-only group were 49% and 16%, respectively, but there was no statistical significance, likely due to the small sample size (p=0.411, multivariate analysis). The difference of age distribution between the CCRT group and the radiation-only group might affect outcome, because this study was a retrospective analysis. To verify the effect of chemotherapy on isolated locoregional recurrent NSCLC, prospective randomized trials are needed.

At present, grading system of lung toxicity is classified according to the severity of symptoms, rather than parameters of PFT. Nevertheless, many researchers have investigated the relationship between PFT and lung complications after radiation to lung. In general, a decrease in FEV1 reflects overall lung obstruction, whereas a decrease in DLCO is affected by partial lung diffusion impairment. In this study, a decline of lung function after salvage radiation was evident to some extent.

Compared with baseline pulmonary function, FEV1 and DLCO after salvage radiation decreased, and was especially statistically significant in DLCO (p=0.033). Several studies also reported a reduction in the diffusing capacity of lung after radiation (22-25). Therefore, when considering salvage radiation for loco-regional recurrent NSCLC, pulmonary function should be carefully evaluated to avoid serious lung complications, and strategies are needed to prevent lung damage.

Curative radiotherapy for locoregional recurrence of NSCLC after surgical resection is effective in terms of survival, and could achieve a comparable outcome for patients with newly-diagnosed NSCLC. When considering radiotherapy, lung function should be carefully evaluated to avoid serious lung damage. The role of chemotherapy combined with radiotherapy for locoregional recurrent NSCLC needs to be studied further.

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